A Regio- and Stereo-selective Free Radical Bromination of Steroidal αβ-Unsaturated Ketones

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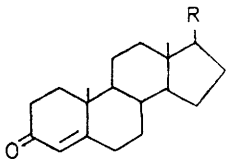
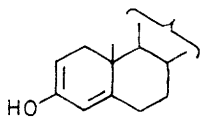
The light catalysed bromination of αβ-unsaturated steroidal ketones has been studied in the presence of an epoxide as a hydrobromic acid scavenger. In these conditions an uncommon regio- and stereo-selectivity for a radical reaction is observed and only 6β-brominated products are formed.

It is known [1-4] that the bromination of steroidal αβ-unsaturated ketones such as cholest-4-en-3-one (1a) leads to a complicated mixture of 2-, 4-, and 6-substituted products amongst other isomeric and dibrominated compounds and, depending on the reaction conditions, one or more products can predominate. These reactions are complicated because the various tautomeric forms of the substrate [(1)—(3)] are susceptible to electrophilic attack.

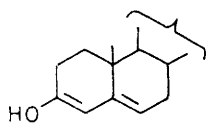


(1)



(2)

a; R = C_8H_{17}
b; R = $COCH_3$



(3)

Thus, notwithstanding the work devoted to this subject, the factors which govern the regio- and stereo-selectivity of the entering electrophile are still obscure. Only the origin of the 4-substituted product, resulting from an addition–elimination sequence to the double bond of unenolized (1a), is clear, as suggested by Kirk *et al.*[5] and confirmed later by de la Mare and Hannan.[6]

Recently it was shown [6] that bromination in acetic acid of (1a) is a rapid autocatalytic process and yields a mixture almost entirely formed by the 6β- and 6α-epimers. But it is difficult to establish the path of this latter reaction as an ionic process through the addition of bromine to the more stable enol (3). In fact during the enolization of (1a) catalysed by hydrobromic acid, the less stable enol (2) should be formed more rapidly and, before its isomerization to the more stable enol (3), it should react with bromine to give almost completely the 2-substituted products.† According this hypothesis we showed [8] that bromination of (1a) catalysed by HCl in ether, as solvent, and with a very low bromine concentration compared with that of the enols, yields only 2-substituted cholest-4-en-3-one.

In connection with other studies [9] on the possibility that the halogenation of ketones with bulk concentrations of halogens, could occur by two competitive, ionic and radical, mechanisms, we supposed that some 6-substituted products could arise during the usual brominations of unsaturated steroidal ketones at least in part from a free radical mechanism.

In order to verify this idea it is necessary to use a solvent with low polarity and low solvating power to avoid any ionic addition–elimination to the double bond of (1a).[5,6] It is also necessary to use bulk concentrations of bromine as usual, but with simultaneous fast neutralization of the hydrobromic acid produced to avoid any acid-catalysed formation of enols (2) and (3), or isomerization of the initially formed products.[6] All these conditions are satisfied if the bromination of (1a) is carried out with stoicheiometric amounts of the reactants in carbon tetrachloride and in the presence of cyclohexene oxide as the acid scavenger. In the dark, bromination is completely inhibited and after 3 weeks the starting ketone can be isolated. But if the reaction is exposed to the light from a 100 W tungsten lamp, the ketone reacts quite rapidly to give only 6β-bromocholest-4-en-3-one together with cyclohexane bromohydrin as byproduct. The free radical character of this reaction was strengthened by the bromination under the same conditions of progesterone (1b) where, notwithstanding the presence of two carbonyl groups so that more tautomeric forms of the substrate are susceptible to electrophilic attack, again only the 6β-epimer can be isolated.

These results throw some light on the reaction paths which may be summarized as follows. (*i*) Acid-catalysed bromination of these ketones with low halogen concentration compared with that of the kinetically favoured enol (2), yields the 2-substituted epimers. (*ii*) If the

† For the acid-catalysed isomerization of the more rapidly formed enol (2) to (3) the sequence (2) ⇌ (1) ⇌ (3) is followed but the bromination of (2) should be faster than its ketonization to (1). For example Dubois and Toullec [7] reported a ketonization : bromination ratio of 10^{-6} for acetone enol.

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ketone reacts with bulk concentrations of bromine and in a nucleophilic solvent such as acetic acid in the presence of proton acceptors such as collidine, addition–elimination to the double bond of the unenolized ketone predominates and the 4-substituted product should be isolated. (*iii*) Finally in apolar solvents and with very low hydrobromic acid concentrations, the free radical path leading to the 6-substituted product predominates. Obviously it is possible that during bromination in acetic acid all three mechanisms are operating and the three possible products are produced simultaneously.

In conclusion while some aspects, *e.g.* the stereoselectivity of the radical mechanism, are not fully understood, the importance of acid, bromine concentration, and solvent in favouring almost exclusively one or other product, permits a simple solution of the problem of directive effects in bromination of αβ-unsaturated steroidal ketones and avoids the use of more complex reactions.

EXPERIMENTAL

Bromination of Cholest-4-en-3-one.—Compound (1a) (0.764 g), bromine (0.318 g, 1 mol. equiv.), and cyclohexene oxide (0.30 g, 1.5 mol. equiv.) were dissolved in dry carbon tetrachloride (40 ml) and exposed to light from a 100 W tungsten lamp. After 4 h the solution was chromatographated (silica gel, eluant light petroleum–ether 5 : 3) and yielded pure 6β-bromocholest-4-en-3-one (0.732 g, 80%), m.p. 134—135° (lit.,[10] 134—135°); $\lambda_{max.}$ ($CHCl_3$) 250 nm, τ (CCl_4) 4.25 (4 H, s), 5.10br (6 H), and 8.46 (s, 19·H_3). By-products isolated were unchanged epoxide, cyclohexane bromohydrin, and starting ketone.

Bromination of Progesterone.—Progesterone (1.88 g), bromine (0.95 g, 1 mol. equiv.), and cyclohexane epoxide (0.88 g, 1.5 mol. equiv.) were dissolved in CCl_4 (120 ml). After exposure to light for 15 h, 6β-bromoprogesterone (1.35 g) was precipitated and filtered off; m.p. 149—150° (lit.,[11] 143—145°), $\lambda_{max.}$ (ethanol) 248 nm, $\nu_{max.}$ 1 700 and 1 670 cm^{-1}, τ ($CDCl_3$) 4.15 (4 H, s), 5.08br (6 H), and 8.48 (s, 19-H_3). The filtrate, after chromatography on silica gel (eluant light petroleum–ether–acetone 3 : 9 : 1) yielded more 6β-compound (0.7 g; overall yield 87%) with some unchanged progesterone.

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